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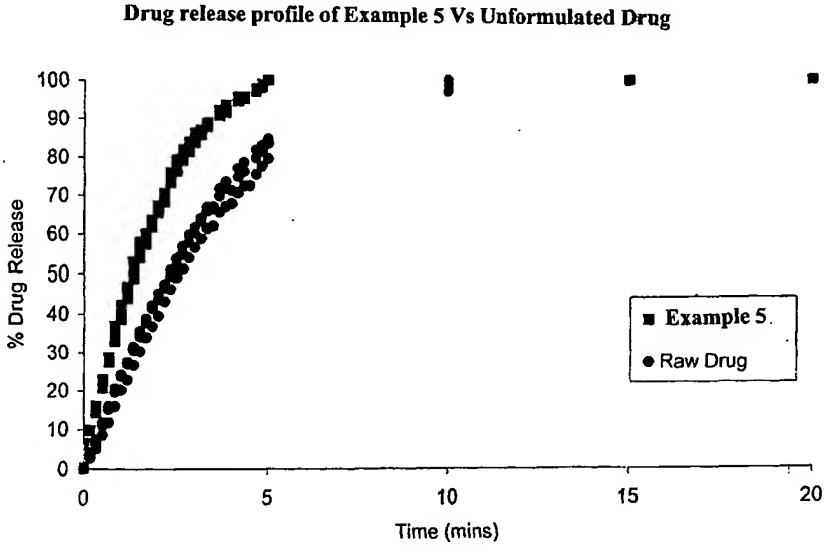
(54) Title: FAST MELT MULTIPARTICULATE FORMULATIONS FOR ORAL DELIVERY



(57) Abstract: A drug formulation for gastrointestinal deposition, said formulation comprising a free flowing plurality of particles comprising an active agent and a water-soluble excipient, wherein the particles have a mean diameter of greater than about 10 μm to about 1 mm, and the formulation is capable of dissolving or dispersing in a patient's mouth within 1 minute after administration without the co-administration of a fluid.

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Fast Melt Multiparticulate Formulations For Oral Delivery

Description

The present is directed to fast melt multiparticulate formulations for oral use. The multiparticulates can be used in a multiple dose delivery device which dispenses a unit dose of the powder upon actuation, or can be packaged for dispensation in sachets or like unit dose containers.

The most prominent mode of delivery of therapeutic agents is by the oral route by means of solid dosage forms such as tablets and capsules. Oral administration of solid dosage forms is more convenient and accepted than other modes of administration, e.g., parenteral administration. However, the manufacture, dispensing and administration of solid dosage forms are not without associated problems and drawbacks.

With the manufacture of solid dosage forms, in addition to the active agent, it is necessary to combine other ingredients in the formulations for various reasons, such as to enhance physical appearance, to provide necessary bulk for tableting or capsuling, to improve stability, to improve compressibility or to aid in disintegration after administration. However, these added excipients have been shown to adversely influence the release, stability and bioavailability of the active ingredient. The added excipients are a particular problem with drugs which require a high dose in order to provide a therapeutic effect, e.g., biphosphonate drugs. The inclusion of the additional excipient can make the final tablet extremely large which could result in esophogeal damage due to the physical characteristics of the dosage form if it is not swallowed properly. Esophogeal damage can also be caused by toxicity caused by the drug itself, if the tablet becomes lodged in the throat or has an increased transit time through the esophagus, due to its increased size.

Further, the tableting of certain drugs has many associated production problems. In particular, many drugs, e.g., paracetamol (acetaminophen), have poor compressibility and cannot be directly compressed into solid dosage forms.

Consequently, such drugs must either be wet granulated or manufactured in a special grade in order to be tableted which increases manufacturing steps and production costs.

The adherence to good manufacturing practices and process controls is essential in order to minimize dosage form to dosage form and batch to batch variations of the final product. Even strict adherence to these practices still is not a guarantee that acceptable variation will occur.

With the high cost of industrial scale production and governmental approval of solid dosage forms, such formulations are often available in a limited number of strengths, which only meet the needs of the largest sectors of the population. Unfortunately, this practice leaves many patients without acceptable means of treatment and physicians in a quandary with respect to individualizing dosages to meet the clinical needs of their patients.

The dispensing of oral solid dosage forms also makes the formulations susceptible to degradation and contamination due to repackaging, improper storage and manual handling.

There are also many patients who are unable or unwilling to take conventional orally administered dosage forms. For some patients, the perception of unacceptable taste or mouth feel of a dose of medicine leads to a gag reflex action that makes swallowing difficult or impossible. Other patients, e.g., pediatric and geriatric patients, find it difficult to ingest typical solid oral dosage forms, e.g., due to tablet size.

Other patients, particularly elderly patients, have conditions such as achlorhydria which hinders the successful use of oral solid dosage forms. Achlorhydria is a condition wherein there is an abnormal deficiency or absence of free hydrochloric acid in the gastric secretions of the stomach. This condition hinders the disintegration and/or dissolution of oral solid dosage forms, particularly dosage forms with high or insoluble excipient payloads. Thus, as the present dosage form

is in fast melt multiparticulate form, it does not need to undergo disintegration and/or dissolution to the same extent as solid dosage forms

Flavoured solutions/suspensions of some therapeutic agents have been developed to facilitate the oral administration of oral agents to patients normally having difficulty ingesting conventional solid oral dosage forms. While liquid formulations are more easily administered to the problem patient, liquid/suspension formulations are not without their own significant problems and restrictions. The liquid dose amount is not as easily controlled compared with tablet and capsule forms and many therapeutic agents are not sufficiently stable in solution/suspension form. Indeed, most suspension type formulations are typically reconstituted by the pharmacist and then have a limited shelf life even under refrigerated conditions. Another problem with liquid formulations which is not as much a factor with tablets and capsules is the taste of the active agent. The taste of some therapeutic agents is so unacceptable that liquid formulations are not a viable option. Further, solution/suspension type formulations are typically not acceptable where the active agent must be provided with a protective coating, e.g. a taste masking coating or an enteric coating to protect the active agent from the strongly acidic conditions of the stomach.

Fast melt drug formulations have also been developed to facilitate the oral administration of oral agents to patients normally having difficulty ingesting conventional solid oral dosage forms. Fast melt formulations are typically in the form of tablets or lozenges that dissolve or disperse in a patient's mouth within a minute without the need of water or chewing. Drug delivery formulations which exhibit fast melt properties can improve patient compliance due to the ease of swallowing as well as the absence of a need for the co-administration of water or another fluid. Further, fast melt systems can be formulated as to have a superior taste and improved accuracy of dosing as compared to liquid preparations.

Other formulations which have been contemplated in order to facilitate the oral administration of oral agents and to avoid the associated problems of solid dosage forms are multiparticulate dosage forms as disclosed in WO 01/64182, the contents of which are hereby incorporated by reference.

According to a first aspect of the present invention, there is provided a drug formulation for gastrointestinal deposition, said formulation comprising a free flowing plurality of particles comprising an active agent and a water-soluble excipient, wherein the particles have a mean diameter of greater than about 10 μm to about 1 mm, and the formulation is capable of dissolving or dispersing in a patient's mouth within 1 minute after administration without the co-administration of a fluid.

Thus, the present invention, in its first aspect, provides a formulation which exhibits the benefits of fast melt formulations as well as the benefits of multiparticulate formulations. It also facilitates the delivery of a wide range of therapeutic agents for gastrointestinal deposition and minimizes pulmonary deposition of materials having undesirable or unknown pulmonary toxicology but which are approved for oral delivery. In some embodiments, the formulation can contain minimal excipient and be used in a multiple dose delivery device which dispenses a unit dose of the formulation upon actuation. Such delivery devices are disclosed in WO 01/64182.

In a second aspect, the present invention provides a drug formulation for gastrointestinal deposition, said formulation comprising a free flowing plurality of particles and including an active agent and a water-soluble excipient, wherein the particles have a mean diameter of greater than about 10 μm to about 1 mm, and the excipient has a negative heat of solution.

A significant advantage of formulations in accordance with the second aspect of the invention is that, when administered via the oral cavity, the local cooling caused by the water-soluble excipient dissolving in saliva serves to mask the taste of the active agent in a manner which does not delay the release, or dissolution of the active agent itself.

Preferably, formulations in accordance with the second aspect of the invention are capable of dissolving or dispersing in a patient's mouth within one minute after

administration, without the co-administration of a fluid. Such preferred formulations, therefore, are also examples of the first aspect of the invention and will provide all of the aforementioned benefits associated with the first aspect of the invention.

Drug formulations in accordance with either the first or the second aspect of the invention are preferably arranged for direct, un-encapsulated administration to a patient's oral cavity. It is also preferred for the particles to be non-compressed.

In embodiments, the particles each include both active agent and water-soluble excipient. The particles can comprise a core and a coating, with the coating including a quantity of the water-soluble excipient.

Preferably, and in accordance with either aspect of the invention, the particles are formed by melt-coating core particles with a coating material that includes (and may consist of) a quantity of the excipient, at a temperature below that at which the active agent melts or decomposes. Forming the particles in this manner is considered to provide them with surface properties that render them easily wetted and capable of rapidly absorbing water from their environment and, thus, able to facilitate the rapid dissolution or dispersion of the formulation, especially the active agent, when the formulation is exposed to an aqueous environment, such as in the oral cavity.

A quantity of the active agent can be included in the core or core particles and/or in the coating or coating material. In some preferred embodiments, the coating or coating material is substantially free of active agent, whereas in others, the core is substantially free of active agent.

In further embodiments of either aspect of the invention, the coating or coating material comprises a water-soluble or hydrophilic binder. Preferably, the binder melts or softens sufficiently to melt-coat the core particles at a temperature below that at which the active agent melts or decomposes. In further embodiments, the water-soluble excipient melts or softens sufficiently to melt-coat the core particles

at a temperature below that at which the active agent melts or decomposes. In further preferred arrangements, the binder melts or softens sufficiently to melt-coat the core particles at a temperature below that at which the water-soluble excipient melts or decomposes.

In some embodiments of the invention, the coating or coating material substantially completely covers the surface of the core or core particles.

Thus, particles in accordance with the present invention can comprise a core that consists substantially or entirely of active agent surrounded by a coating that comprises water-soluble excipient either alone, or in combination with a water-soluble or hydrophilic binder. When the water-soluble excipient is employed alone in such particles, it is preferred for it to be capable of melting or softening sufficiently to melt-coat the core particles at a temperature below that at which the active agent melts or decomposes. Where a binder is employed, the water-soluble excipient need not be capable of melting or softening at a temperature below the melting or decomposition temperature of the active agent. However, when such a high melting point water-soluble excipient is employed, the binder should be capable both of melting or softening sufficiently to melt-coat the core particles at a temperature below that at which the active agent melts or decomposes, and of binding the water-soluble excipient in the coating.

The core or core particles, in addition to including active agent, can also include a quantity of the water-soluble excipient and/or an additional excipient, which may also be water soluble, but which does not necessarily qualify as a water-soluble excipient in accordance with the present invention. For example, the core can comprise a granulation of such an additional excipient (e.g. polyvinyl alcohol, or polyvinylpyrrolidine) and active agent, or consist of a particle (e.g. a microcrystalline cellulose sphere) of additional excipient coated with active agent.

In other embodiments in accordance with the invention, the core can consist entirely of water-soluble excipient. In such embodiments, the coat or coating material comprises active agent and either an additional quantity of water-soluble

excipient, or a binder. When the coat or coating material comprises active agent and binder, additional water-soluble excipient can also be present in therein.

It is preferred that formulations in accordance with either aspect of the present invention are formed by a process in which the active agent is not raised to or above its melting point, or a temperature at which a significant proportion thereof is caused to decompose.

The melting point of the water-soluble excipient is preferably equal to or below 150, 120 or 110°C, and is preferably at least 40 or 50°C. Preferably, the excipient melts at around or below 100°C. The melting point of the binder, if employed, is preferably equal to or below 150, 120 or 110°C, and is preferably at least 40 or 50°C. More preferably, the binder melts at around or below 100°C. In certain embodiments, the melting point of the excipient exceeds that of the binder.

The water-soluble excipient, preferably, has a heat of solution equal to or below –7KCal/Kg. More preferably, the heat of solution of the water-soluble excipient is equal to or below –10, -15, -20, -25, or -30KCal/Kg. The solubility in water of the water-soluble excipient is preferably at least 20, 30 or 40% w/w at 25°C.

The water-soluble excipient is preferably a sugar, sugar alcohol, polyethylene glycol (PEG), or polyethylene oxide, and is preferably not lactose. Formulations in accordance with the invention, preferably, are lactose free. The preferred water-soluble excipients are the sugar alcohols including, but not limited to sorbitol, mannitol, maltitol, reduced starch saccharide, xylitol, reduced paratinose, erythritol, and combinations thereof. The preferred sugar is glucose. Other suitable water-soluble excipients include gelatin, partially hydrolyzed gelatin, hydrolyzed dextran, dextrin, alginate and mixtures thereof.

Preferred binders include polyethylene glycols (PEG) and polyethylene oxides.

In further preferred embodiments, the core or core particles include an additional excipient for controlling or delaying the release of the active agent. In this regard,

the core or core particles can include a layer or coating of such an additional excipient encapsulating an inner core comprising the active agent. The additional excipient can be selected from those known to persons skilled in the art to be capable of controlling the release of an encapsulated active agent. Such excipients include those commonly used to provide enteric and sustained release coatings. Examples of the former include cellulose acetate phthalate, hydroxypropyl-methylcelluose phthalate, polymethacrylates, such as Eudragit® L 100-55 or L 30 D-55, and Shellac. Examples of the latter include ethylcellulose, hydroxypropyl-celluose, hydroxypropylmethylcelluose, and polymethacrylates, such as Eudragit® RL and RS film-coating systems.

In alternative embodiments, formulations in accordance with the invention can provide rapid release of the active agent. In this regard, the term "rapid release" should be understood to mean that such formulations release at least 80% of their active agent within 45 minutes in standard dissolution tests. In the case of poorly soluble active agents, such formulations typically release at least 80% of their active agent within 40, 30, 20, 15 and preferably 10 minutes after being administered to a patient's oral cavity. In the case of more soluble active agents, such formulations typically release at least 80% of their active agent within 10, 7 and preferably 5 minutes after being administered to a patient's oral cavity. In particularly preferred embodiments of the invention, the active agent will dissolve into an aqueous environment more rapidly from a formulation in accordance with the invention than it would if it had not been incorporated in such a formulation.

In a third aspect, the present invention provides a method of preparing a drug formulation in accordance with the first or second aspect of the invention, comprising forming the particles by melt-coating core particles with a coating material that includes a quantity of the water-soluble excipient, at a temperature below the melting point or decomposition temperature of the active agent.

In a further aspect, the invention provides the use of a drug formulation in accordance with the first or second aspect of the invention, or a drug formulation prepared by a method in accordance with the third aspect of the invention, for the

preparation of a medicament for treating a human or animal patient, wherein the formulation is administered directly and in an un-encapsulated form to the patient's oral cavity. The invention also provides a method of treating a human or animal patient, wherein a formulation in accordance with the first or second aspect of the invention, or prepared by a method in accordance with a third aspect of the invention, is administered in a un-encapsulated form directly into the patient's oral cavity.

It is also possible for formulations in accordance with either the first aspect or the second aspect of the invention to include additional particles with different properties to those described above. For example, the additional particles may not include any active agent.

Certain embodiments of the invention comprise a fast melt multiparticulate formulation which contains a salivary stimulant to facilitate hydration of the formulation and the swallowing of a unit dose of the multiparticulates upon oral delivery.

Certain embodiments of the invention comprise a fast melt multiparticulate formulation which has a desired particle range in order to minimize pulmonary aspiration of particles.

Fast melt multiparticulate formulations in accordance with the invention are, preferably, divisable into unit doses (e.g. with the use of a multiple unit dosing device) with a weight uniformity which is within the acceptable range of weight uniformity for tablets or capsules. A detailed discussion of weight uniformity can be found in the USP/NF 23/18 section 905, which is hereby incorporated by reference in its entirety for all purposes.

The invention also provides methods of preparing fast melt multiparticulate dosage forms and systems disclosed herein. The invention further provides methods of preparing fast melt multiparticulate dosage forms without the use of an aqueous fluid as a processing aid.

The invention additionally provides methods of preparing multiple unit delivery systems containing fast melt multiparticulate dosage forms in accordance with the invention.

The invention also provides methods of preparing fast melt multiparticulate dosage forms having a desired particle size range.

The invention further provides methods of administering an active agent comprising administering a fast melt multiparticulate dosage form.

The invention additionally provides methods of administering an active agent comprising administering a fast melt multiparticulate dosage form via the use of a multiple unit delivery system.

In certain embodiments, the present invention is directed to a drug formulation for gastrointestinal deposition comprising a non-compressed free flowing plurality of particles comprising an active agent and a water-soluble excipient, the particles having a mean diameter of greater than 10 μm to about 1 mm, the particles comprising at least about 50% drug and the formulation dissolving in a patient's mouth within 1 minute after administration without the co-administration of a fluid.

In certain embodiments, the invention is directed to a method of treating a patient with an active agent for gastrointestinal deposition comprising administering a formulation comprising a non-compressed free flowing plurality of particles comprising an active agent and a water-soluble excipient, the particles having a mean diameter of greater than 10 μm to about 1 mm, and the formulation dissolving in a patient's mouth within 1 minute after administration without the co-administration of a fluid.

In certain embodiments, the invention is directed to a drug delivery system for delivery of a drug for gastrointestinal deposition. The system comprises a multiple unit dosing device comprising a housing and an actuator, the device containing

multiple doses of a fast melt multiparticulate formulation, the device upon actuation delivering a unit dose of the fast melt multiparticulates for gastrointestinal deposition, the multiparticulates having a mean particle size of greater than 10 μm and preferably less than about 1mm in order to minimize pulmonary deposition of the multiparticulates and such that an effective dose of the drug cannot be delivered into the lower lung of a human patient. The drug delivery system can be used to administer the unit dose of fast melt multiparticulates into the oral cavity of the patient (*in-vivo*) or to dispense the unit dose into an intermediate receptacle (*ex-vivo*) for subsequent gastrointestinal deposition. Oral drug delivery systems and devices for oral powders are disclosed in WO01/64182, hereby incorporated by reference in its entirety for all purposes.

In certain embodiments, the invention provides a method of preparing a drug delivery system for delivering multiple doses of a drug for gastrointestinal deposition comprising preparing a fast melt multiparticulate drug formulation in a manner wherein the drug particles when placed in the oral cavity are not deposited in any substantial amount to the lungs; and placing multiple unit doses of the fast melt drug formulation in a device which meters a single unit dose for delivery.

In certain embodiments, the invention provides a method of treating a patient in need of multiple doses of a drug for gastrointestinal deposition comprising preparing fast melt multiparticulates in a manner wherein the drug particles when placed in the oral cavity are not deposited in any substantial amount to the lungs and dissolve or disperse in the mouth within 1 minute after administration, placing multiple unit doses of the fast melt multiparticulates in a device which meters a single unit dose for delivery; and either (a) administering the unit dose into the oral cavity of a patient or(b) dispensing the unit dose into an intermediate receptacle and thereafter administering the unit dose into the oral cavity of the patient.

In certain embodiments, the particles of the invention comprise at least about 50% drug; at least about 60% drug; at least about 70% drug; at least about 80% drug; or at least about 90% drug. In others, low doses of up to 20%, 10% or 5% of drug or active agent are carried by the inventive particles. In certain embodiments, the

invention provides a method for delivery of a drug comprising delivering fast melt multiparticulates comprising drug particles via the use of a multiple unit dosing device comprising a housing and an actuator, the device upon actuation delivering a unit dose of the fast melt multiparticulates, and thereafter re-using the device to deliver additional unit doses of the fast melt multiparticulates at appropriate dosing intervals.

In preferred embodiments of the invention, the unit dose comprises a discreet collection of fast melt multiparticulates. For purposes of the invention, a "discreet collection" means that the fast melt multiparticulates are in the form of a non-compressed free flowing unit and not dispersed in a cloud or mist, which effectively minimizes inhalation of the active agent into the lungs of the patient. The unit dose can be include from about 0.01 mg to about 1.5 g of active agent. For example, the dose of active agent can be from about 1 mg to about 100 mg, or from about 10 mg to about 50 mg.

In certain embodiments of the invention, the mean diameter of the fast melt multiparticulates is of a size which minimizes their capacity to be inhaled into the lower lung. Typically, the mean particle size of the drug particles (or agglomerates) is greater than 10 μm, preferably greater than about 50 μm or greater than about 75 μm. In certain embodiments of the invention, the mean particle size range of the drug particles is from about 100 μm to about 1 mm, preferably from about 50 μm to about 500 μm . In preferred embodiments, greater than 80% of the particles have the above disclosed diameter (not mean diameter), e.g. 80% of the drug particles have a diameter of greater than 10 μm, or a diameter of from about 100 μm to about 1 mm. In other embodiments, greater than about 90% of the particles have the above disclosed diameter.

In certain embodiments of the invention, the mean diameter of the fast melt multiparticulates does not vary by greater than about 20%, preferably not greater than about 15% and most preferably not greater than about 10%.

In certain embodiments of the invention, the multiple doses of the fast melt formulation are contained in a reservoir. The reservoir can contain an amount of multiparticulates to provide any number of unit doses, e.g. from about 2 doses to about 400 doses. For ease in patient compliance, the reservoir has a sufficient quantity of to provide e.g. a days supply, a months supply or a years supply of doses, e.g. 30 or 365 for once daily dosing for a month or year, respectively.

In order to aid in patient compliance, certain embodiments of the invention include a counter or indicator to display the number of doses remaining in the system or the number of doses actuated.

In certain embodiments of the invention, the unit doses are individually metered prior to actuation, e.g., in the form of capsules or blisters or preferably in the form of sachets, wherein each sachet contains one individual unit dose. The system can be capable of containing any multiple of pre-metered unit doses, e.g. from about 2 to about 400 sachets.

For purposes of the present invention, the term "device" refers to an apparatus capable of delivering a unit dose of drug.

The term "system" refers to a drug delivery device in combination with a fast melt multiparticulate formulation having the specifications disclosed herein, e.g. drug particle size, excipient type, etc.

The term "discreet collection" refers to a non-compressed free flowing unit of multiparticulates with minimal particulate matter being dispersed in the surrounding environment (e.g., as a cloud or mist).

The term "drug" refers to any agent which is capable of providing a therapeutic effect to a patient upon gastrointestinal deposition. This encompasses all drugs which are intended for absorption for a systemic effect (regardless of their actual bioavailability) as well as drugs intended for a local effect in the gut and /or oral cavity, e.g. nystatin, antibiotics or local anaesthetics.

The term "particle size" refers to the diameter of the particle.

The term "deposition" means the deposit of the unit dose at the intended point of absorption and/or action. For example, gastro-intestinal deposition means the intended deposit of the unit dose in the gastrointestinal system for e.g., absorption for a systemic effect or to exert a local effect. Pulmonary deposition means the intended deposit of drug into the lungs in order to provide a pharmaceutical effect, regardless that the unit dose may enter the oral cavity prior to pulmonary deposition.

The term "dispense", when used in connection with the devices and systems of the present invention, means that the device or system delivers the unit dose *ex vivo* with the intent of subsequent administration to a mammal. For example, the device or system can dispense the unit dose into a food, a liquid, a spoon, or another intermediate receptacle.

The term "administer", when used in connection with the devices and systems of the present invention, means that the device or system delivers the unit dose *in vivo*, i.e., directly into the gastrointestinal tract of a mammal.

The term "deliver" is meant to cover all *ex vivo* and *in vivo* delivery, i.e., dispensing and administering, respectively.

The term "patient" refers to humans as well as other mammals in need of a therapeutic agent, e.g., household pets or livestock. This term also refers to humans or mammals in need of or receiving prophylactic treatment.

The term "fast melt" means a formulation which dissolving or disperses in a patient's mouth within 1 minute after administration without the co-administration of a fluid. Preferably, the formulation dissolving or disperses in a patient's mouth within 30 seconds, or 15 seconds after administration without the co-administration of a fluid

The term "disperses" means that the administered formulation becomes hydrated in the mouth and the particles of the formulation become suspended is saliva, such that the multiparticulate formulation is wetted and easily swallowed.

In certain embodiments, the particulates are defined functionally with respect to the fact that they are of a size such that an effective dose cannot be delivered into the lower lung of a human patient. However, this definition should be understood to mean that a small percentage of drug (but not an amount effective to render a therapeutic effect) may in fact be inadvertently delivered to the lungs of the patient. Also, this definition is meant to define the particles, but not to limit the use of the invention to the treatments of humans only. The invention may be used for delivering doses of drugs to other mammals as well.

In this specification, there are references to the temperature at which the active agent or the water-soluble excipient decomposes. This temperature should be understood to be the temperature at and above which the active agent or excipient would decompose to a significant extent, if held there for sufficient time for the active agent or excipient to be processes by melt granulation.

In general, it has been recognized in the art that dry powder inhalation or insufflation formulations must consist of particles of a size of about 2 microns in diameter in order for the particles, when inhaled, to reach the peripheral or "deep" lung, including alveoli. Particles larger than 10 microns in diameter are not able to reach the deep lung when inhaled because they are collected on the back of the throat and upper airways in humans. Therefore, known powder delivery systems have been formulated with particle sizes of less than 10 microns in order for the particles to reach the intended site of action, the pulmonary system. Known powder delivery devices have not contemplated delivery of particles from a multi-dose delivery device to achieve gastrointestinal deposition, and therefore have avoided the use of drug particles having a large size, e.g. greater than 10 microns. By virtue of the invention disclosed in Applicants co-pending application, WO01/64182, it has been a surprising discovery that drug particles greater than 10

microns can be delivered from a multi-use drug delivery device for gastrointestinal deposition in a patient in order to minimize the inhalation of the drug particles into the lungs, in order to have substantially all of the dose deposited in the gastrointestinal system. By virtue of the present invention, powders that can be used in such devices can exhibit fast melt properties in order to provide the benefits of such formulations. The powders can be used in the device or can be administered without the use of the device, e.g., by using a sachet.

As the fast melt multiparticulates of the present invention are not intended to be compressed, a high load formulation of the active agent is ascertainable. This is due to the fact that excipients which must be included in prior art fast melt tablets (e.g., fillers in order to provide bulk for tableting and disintegrants to provide a breakdown of the tablet upon administration) need not be included in the present formulations, or included to a lesser extent. As the fast melt formulations can have lower excipient and a higher drug load, the resultant unit dose is smaller which decreases the necessary time for the dissolution or dispersion of the formulation upon oral delivery.

The water-soluble excipient of the formulation can be a sugar alcohol including, but not limited to sorbitol, mannitol, maltitol, reduced starch saccharide, xylitol, reduced paratinose, erythritol, and combination thereof. Other suitable water-soluble excipients include gelatin, partially hydrolyzed gelatin, hydrolyzed dextran, dextrin, alginate and mixtures thereof.

The formulations of the present invention preferably include a salivary stimulant including, but not limited to citric acid, tartaric acid, malic acid, fumaric acid, adipic acid, succinic acid, acid anhydrides thereof, acid salts thereof and combinations thereof.

The salivary stimulant can also be an effervescent agent, such as wherein the effervescence is the result of a reaction of a soluble acid source and an alkali metal carbonate or carbonate source. The carbonate sources can be selected from the group consisting of dry solid carbonate and bicarbonate salts such as sodium

bicarbonate, sodium carbonate, potassium bicarbonate and potassium carbonate, magnesium carbonate and sodium sesquicarbonate, sodium glycine carbonate, L-lysine carbonate, arginine carbonate and amorphous calcium carbonate.

The drug formulations of the present invention preferably comprise a sweetener such as a water-soluble artificial sweetener, including but not limited to soluble saccharin salts, such as sodium or calcium saccharin salts, cyclamate salts, acesulfam-K, the free acid form of saccharin and mixtures thereof. The sweetener can also comprise a dipeptide based sweetener such as L-aspartyl L-phenylalanine methyl ester.

The formulations of the present invention can also comprise further pharmaceutical excipients such as polyvinyl alcohol, polyvinylpyrrolidine, acacia or a combination thereof.

The dissolution or dispersion of the formulation can be improved with the use of a surfactant, such as sodium lauryl sulphate (Texapon K 12), various polysorbates known under the trade name Tween, ethers of polyhydroxy ethylene fatty acids known under the trade name Brij, esters of polyhydroxy ethylene fatty acids known under the trade name Myrj, sodium desoxycholate, glycerol polyethylene glycol ricinoleate (Cremophor EL), polyoxyethylene-polyoxypropylene polymers known under the trade name Pluronic, and various polyalkoxy alkylene sterol ethers.

The fast melt formulations of the present invention can also comprise starches, e.g., corn starch, or modified starches, e.g., sodium starch glycolate or mixtures thereof, in any proportions. Starches can provide increased salivation due to the porous nature of the starch. Increased salivation favours rapid dissolution or dispersion of the formulation upon oral administration.

When a starch is present in the formulation, the formulation can further comprise a starch degrading enzyme will have a synergistic effect with the starch with respect to dissolution or dispersion. The enzymes upon being contacted with an aqueous solution will initiate conversion of the starch to mono and polysaccharides which

quickly dissolve in the aqueous environment and further contribute to improving the taste of the multiparticulate formulation and increasing salivation.

The enzymes can be chosen for their degradation effect on the starch and also for their stability over time, i.e. during the shelf-life of the fast melt multiparticulate formulation. Advantageously, the enzyme will be chosen from the group of starch degrading enzymes comprising alpha-amylase, beta-amylase, amyloglucosidase, debranching enzymes and glucose-fructose isomerase. In certain embodiments, the enzymes can be an equal mixture of amyloglucosidase and a-amylase.

In certain embodiments, drug formulations in accordance with the invention are prepared by a process comprising melt granulating the water soluble excipient and the active agent to form a homogenous mixture. In an alternate embodiment, the process comprises melt coating the water-soluble excipient onto the active agent which can be optionally pregranulated with a pharmaceutically acceptable excipient. In such processes, the water-soluble excipient is preferably a water-soluble alcohol such as xylitol.

The melt granulation and melt coating processes are particularly preferred processes of the present invention as it is not necessary to use an aqueous fluid as a processing aid. This results in a process which can be used for a wide variety of active agents, including those agents which would be susceptible to degradation upon contact with water. Accordingly, such processes provide advantages over many prior art processes for making fast melt systems which rely on water as a processing aid. These prior art processes would not be suitable for water liable drugs as such processes would result in degradation of the drug during the manufacturing process and during storage due to residual moisture in the final product.

In certain embodiments, formulations in accordance with the invention can be prepared by subliming solvent from a composition comprising the active agent and the water soluble excipient and reducing the sublimed composition to the particles. In such embodiments, the composition can further comprises an excipient selected

from the group consisting of polyvinyl alcohol, polyvinylpyrrolidone, acacia or a combination thereof. The sublimation is preferably by freeze-drying and the solvent can be an aqueous solvent or a co-solvent comprising an aqueous solvent and an alcohol. A surfactant can also be included in such a formulation.

In certain embodiments, fast melt formulations in accordance with the invention can be prepared by a process which comprises preparing a mixture comprising the active agent, the water soluble excipient and a solvent, freezing the mixture, vacuum drying the frozen mixture above a collapse temperature of the mixture to form a partially collapsed matrix network and reducing the sublimed composition to the particles. Preferably, the mixture comprises the active agent, a gum, a carbohydrate base, and a solvent, wherein the gum is selected from the group consisting of acacia, guar, xanthan, tragacanth gum, and mixtures thereof, and the carbohydrate is selected from the group consisting of mannitol, dextrose, sucrose, lactose, maltose, maltodextrin, corn syrup solids, and mixtures thereof.

In certain embodiments, fast melt formulations in accordance with the invention can be prepared by a process which comprises preparing a mixture comprising the active agent, the water soluble excipient and an agar aqueous solution, solidifying the mixture into a jelly form, drying the jelly and reducing the dried composition into the particles. The drying can be effected by reduced pressure drying, aeration drying or freeze-drying.

In certain embodiments, fast melt formulations in accordance with the invention can be prepared by a process which comprises melt spinning the active agent with the saccharide to form a mass of spun fibres and reducing the spun fibres to the particles. The saccharide can be sucrose or glucose.

In order to achieve the desired lower limit of the particles size of the fast melt multiparticulate formulation of the invention, air jet sieving can be used to remove fine particles. In particular embodiments, the invention is directed to a method of preparing a multiparticulate drug formulation for gastrointestinal deposition comprising preparing a non-compressed free flowing plurality of particles

comprising a core comprising a drug and a pharmaceutically acceptable excipient as disclosed herein and air jet sieving the particles to separate the cores from fine particles; and thereafter overcoating the core with a functional coating as disclosed herein.

The invention is also directed to compositions obtained using these methods.

The compositions of multiparticulates obtained using air jet sieving and methods thereof are not limited to the particular embodiments disclosed herein. The use of an air jet sieve is beneficial as the standard sieving techniques used with screens and meshes may not separate all of the desired fine particles as the fine particles may adhere to the surface of larger particles and thus not separate during the sieving process. The air jet sieving process utilizes a negative pressure to draw particles below a particular size range down through an appropriate screen or mesh. In another embodiment, there is a combination of a downward negative pressure and an upward positive pressure which facilitates the de-agglomeration of the different particle sizes. In other embodiments, the upward pressure can be introduced upwards from a rotating wand. An apparatus utilizing a negative downward pressure and an upward positive pressure through a rotating wand is a Micron Air Jet Sieve MAJS I/II manufactured by Hosakawa.

The effect of humidity can have a negative impact of the flowability of particles (e.g., due to cohesiveness). This can be a particular problem with the present invention, which is directed to fast melt multiparticulates which are designed to absorb water. Accordingly, in preferred embodiments, the unit doses of fast melt multiparticulates are premetered prior to actuation of the device. This reduces the contamination of the unit doses as compared to having the formulation in a multiple dose reservoir. Preferably, the premetered unit doses are contained in sachets which minimize the effect of humidity and moisture on the formulation.

Other multiple unit oral dosing devices, adapted contain the formulation in a reservoir or as premetered unit doses, which are useful in the present invention are disclosed in WO01/64182 hereby incorporated by reference.

Classes of drugs which are suitable in the present invention include antacids, anti-inflammatory substances, coronary dilators, cerebral dilators, peripheral vasodilators, anti-infectives, psychotropics, anti-manics, stimulants, anti-histamines, laxatives, decongestants, vitamins, gastro-intestinal sedatives, anti-diarrheal preparations, anti-anginal drugs, vasodilators, anti-arrhythmics, anti-hypertensive drugs, vasoconstrictors and migraine treatments, anti-coagulants and anti-thrombotic drugs, analgesics, anti-pyretics, hypnotics, sedatives, anti-emetics, anti-nauseants, anti-convulsants, neuromuscular drugs, hyper- and hypoglycemic agents, thyroid and anti-thyroid preparations, diuretics, anti-spasmodics, uterine relaxants, mineral and nutritional additives, anti-obesity drugs, anabolic drugs, erythropoietic drugs, anti-asthmatics, bronchodilators, expectorants, cough suppressants, mucolytics, drugs affecting calcification and bone turnover and anti-uricemic drugs. Specific drugs include gastro-intestinal sedatives such as metoclopramide and propantheline bromide; antacids such as aluminum trisilicate, aluminum hydroxide, ranitidine and cimetidine; anti-inflammatory drugs such as phenylbutazone, indomethacin, naproxen, ibuprofen, flurbiprofen, diclofenac, dexamethasone, prednisone and prednisolone; coronary vasodilator drugs such as glyceryl trinitrate, isosorbide dinitrate and pentaerythritol tetranitrate; peripheral and cerebral vasodilators such as soloctidilum, vincamine, naftidrofuryl oxalate, co-dergocrine mesylate, cyclandelate, papaverine and nicotinic acid; anti-infective substances such as erythromycin stearate, cephalexin, nalidixic acid, tetracycline hydrochloride, ampicillin, flucloxacillin sodium, hexamine mandelate and hexamine hippurate; neuroleptic drugs such as flurazepam, diazepam, temazepam, amitryptyline, doxepin, lithium carbonate, lithium sulfate, chlorpromazine, thioridazine, trifluperazine, fluphenazine, piperothiazine, haloperidol, maprotiline hydrochloride, imipramine and desmethylimipramine; central nervous stimulants such as methylphenidate, ephedrine, epinephrine, isoproterenol, amphetamine sulfate and amphetamine hydrochloride; antihistamic drugs such as diphenhydramine, diphenylpyraline, chlorpheniramine and brompheniramine; anti-diarrheal drugs such as bisacodyl and magnesium hydroxide; the laxative drug, dioctyl sodium sulfosuccinate; nutritional supplements such as ascorbic acid, alpha tocopherol, thiamine and pyridoxine; anti-spasmodic drugs such as dicyclomine and diphenoxylate; drugs affecting the rhythm

of the heart such as verapamil, nifedipine, diltiazem, procainamide, disopyramide, bretylium tosylate, quinidine sulfate and quinidine gluconate; drugs used in the treatment of hypertension such as propranolol hydrochloride, guanethidine monosulphate, methyldopa, oxprenolol hydrochloride, captopril and hydralazine; drugs used in the treatment of migraine such as ergotamine; drugs affecting coagulability of blood such as epsilon aminocaproic acid and protamine sulfate; analgesic drugs such as acetylsalicylic acid, acetaminophen, codeine phosphate, codeine sulfate, oxycodone, dihydrocodeine tartrate, oxycodeinone, morphine, heroin, nalbuphine, butorphanol tartrate, pentazocine hydrochloride, cyclazacine, pethidine, buprenorphine, scopolamine and mefenamic acid; anti-epileptic drugs such as phenytoin sodium and sodium valproate; neuromuscular drugs such as dantrolene sodium; substances used in the treatment of diabetes such as tolbutamide, disbenase glucagon and insulin; drugs used in the treatment of thyroid gland dysfunction such as triiodothyronine, thyroxine and propylthiouracil, diuretic drugs such as furosemide, chlorthalidone, hydrochlorthiazide, spironolactone and triamterene; the uterine relaxant drug ritodrine; appetite suppressants such as fenfluramine hydrochloride, phentermine and diethylproprion hydrochloride; anti-asthmatic and bronchodilator drugs such as aminophylline, theophylline, salbutamol, orciprenaline sulphate and terbutaline sulphate; expectorant drugs such as guaiphenesin; cough suppressants such as dextromethorphan and noscapine; mucolytic drugs such as carbocisteine; anti-septics such as cetylpyridinium chloride, tyrothricin and chlorhexidine; decongestant drugs such as phenylpropanolamine and pseudoephedrine; hypnotic drugs such as dichloralphenazone and nitrazepam; anti-nauseant drugs such as promethazine theoclate; haemopoietic drugs such as ferrous sulphate, folic acid and calcium gluconate; uricosuric drugs such as sulphinpyrazone, allopurinol and probenecid; and calcification affecting agents such as biphosphonates, e.g., etidronate, pamidronate, alendronate, residronate, teludronate, clodronate and alondronate.

Particularly preferred agents include antibiotics such as clarithromycin, amoxicillin erythromycin, ampicillin, penicillin, cephalosporins, e.g., cephalexin, pharmaceutically acceptable salts thereof and derivatives thereof.

A particularly preferred agent is paracetamol (acetaminophen). Other preferred agents are NTHES such as ibuprofen, indomethacin, aspirin, diclofenac and pharmaceutically acceptable salts thereof.

In certain preferred embodiments, however, formulations in accordance with the invention do not include any non-steroidal anti-inflammatory drug (NSAID).

The size of the unit dose is dependent on the amount of drug needed to provide the intended therapeutic effect and the amount of any pharmaceutically acceptable excipient which may be necessary. Typically, a unit dose of from about .01 mg to about 1.5 g would be sufficient to contain a therapeutically effective amount of the drug to be delivered, however, this range is not limiting and can be smaller or higher, depending on the amount of drug and excipient that is necessary.

The following examples serve to illustrate the invention, but should not be understood to be limiting in any respect.

Example 1

The following materials were employed in this example.

Material	% Composition
Paracetamol	75
Xylitol	24
Aspartame	0.5
Acesulphame K	0.5

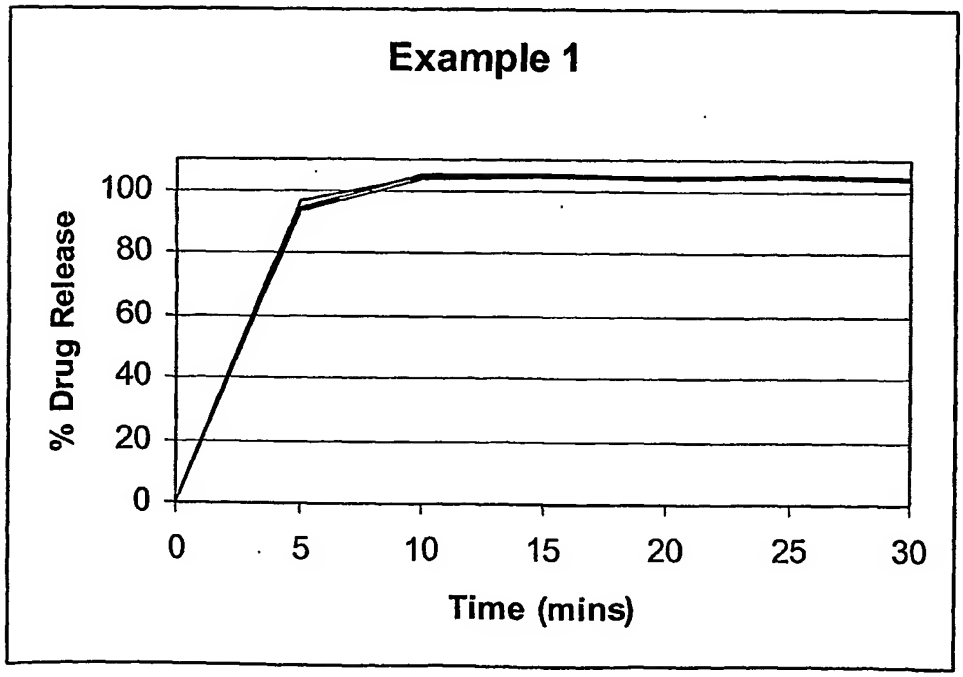
Method

Granular paracetamol, aspartame fine, acesulphame potassium and 12% xylitol were accurately weighed into a glass jar and blended at 42rpm for 30 minutes using an inversion low shear mixer. The blend was transferred to a jacketed vessel maintained at a temperature of 95°C. The blend was mixed at an impeller speed sufficient to keep the whole powder bed moving (i.e. 222RPM) using an overhead

mixer for a time sufficient to allow homogenous distribution of the molten binder in the blend. The remaining melt binder was added to the blend and the impeller speed increased to provide continuous movement of the powder bed (i.e. 250RPM). The formulation was cooled and then sieved using a 710micron sieve to remove any large agglomerates, once distribution of the melt binder was complete.

Results

The formulation had a sweet taste and good mouthfeel. The dissolution of the paracetamol from the formulation was measured using a modified version of the standard USP test for measuring paracetamol (acetaminophen) dissolution. The test conditions involved stirring 333 mg of the formulation in 900ml of water, buffered to pH5.8 with a potassium phosphate buffer, at.37°C, using a paddle speed of 100RPM (the standard USP paddle speed is 50RPM). The results are set out below.



Example 2

The following materials were employed in this example.

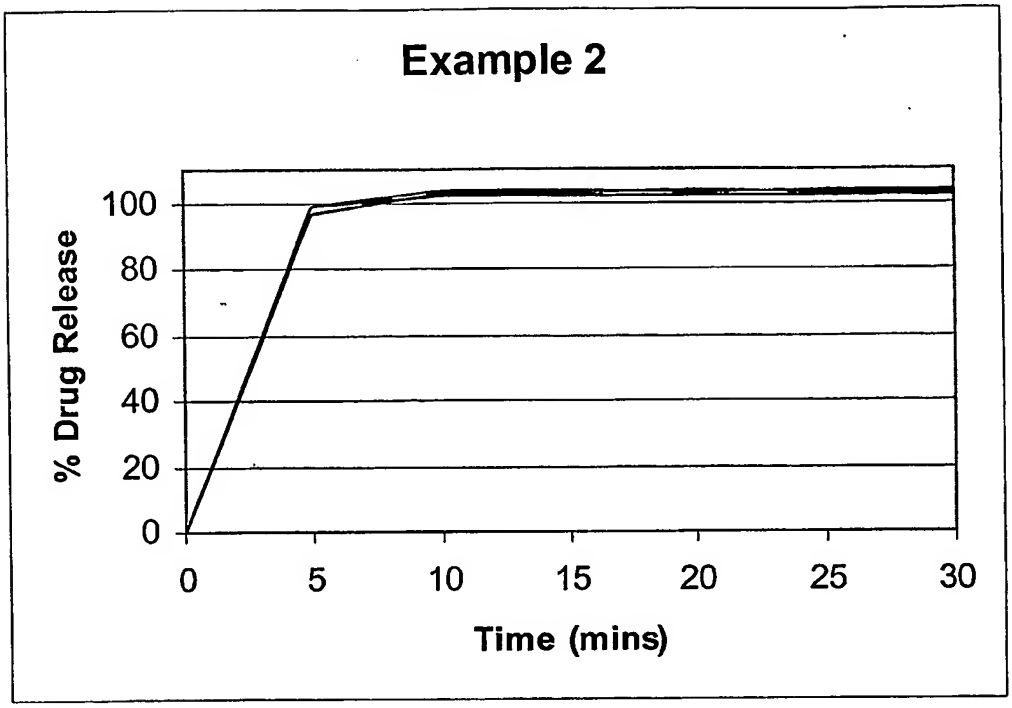
Material	% Composition
Paracetamol	77
Xylitol	20
Aspartame	0.5
Acesulphame K	0.5
Maltodextrin M100	2

Method

Granular paracetamol, aspartame fine, maltodextrin M100, acesulphame potassium and 10% xylitol were accurately weighed into a glass jar and blended at 42rpm for 30 minutes using an inversion low shear mixer. The blend was transferred to a jacketed vessel maintained at a temperature of 95°C. The blend was mixed at an impeller speed sufficient to keep the whole powder bed moving (i.e. 222RPM) using an overhead mixer for a time sufficient to allow homogenous distribution of the molten binder in the blend. The remaining melt binder was added to the blend and the impellar speed increased to provide continuous movement of the powder bed (i.e. 250RPM). The formulation was cooled and then sieved using a 710micron sieve to remove any large agglomerates, once distribution of the melt binder was complete.

Results

It was found that incorporation of certain grades maltodextrin improved mouthfeel and reduced aftertaste without impeding drug release. The dissolution of the paracetamol from the formulation was measured using the same test as that employed in Example 1, and the results are set out below.



Example 3

The tastemasking properties of xylitol result from its negative heat of solution, which confers a cooling effect on dissolution on the oral cavity. This example details the use of erythritol, which has a greater negative heat of solution, to improve the degree of tastemasking. Formulations were prepared using erythritol as the melt binder from the following materials.

Material	% Composition
Paracetamol	87
Erythritol	10
Aspartame	0.5
Acesulphame K	0.5
Maltodextrin M100	2

Method

Granular paracetamol, aspartame fine, maltodextrin M100, acesulphame potassium and 5% erythritol were accurately weighed into a glass jar and blended at 42rpm for 30 minutes using an inversion low shear mixer. The blend was transferred to a jacketed vessel maintained at a temperature of 121°C. The blend was mixed at an impellar speed sufficient to keep the whole powder bed moving (i.e. 222RPM) using an overhead mixer for a time sufficient to allow homogenous distribution of the molten binder in the blend. The remaining melt binder was added to the blend and the impellar speed increased to provide continuous movement of the powder bed (i.e. 250RPM). The formulation was cooled and then sieved using a 710micron sieve to remove any large agglomerates, once distribution of the melt binder was complete.

Results

Upon melt granulation it was observed that the formulation developed a slight brown discoloration. This was attributed to the thermal degredation of Maltodextrin M100. This was confirmed by the preparation of Example 4 in which there was no evidence of browning.

Example 4

The following materials were employed in this example.

Material	% Composition
Paracetamol	89
Erythritol	10
Aspartame	0.5
Acesulphame K	0.5

Method

Granular acetaminophen, aspartame fine, acesulphame potassium and 5% erythritol were accurately weighed into a glass jar and blended at 42rpm for 30 minutes using an inversion low shear mixer. The blend was transferred to a jacketed vessel maintained at a temperature of 121°C. The blend was mixed at an impeller speed

sufficient to keep the whole powder bed moving (i.e. 222RPM) using an overhead mixer for a time sufficient to allow homogenous distribution of the molten binder in the blend. The remaining melt binder (erythritol) was added to the blend and the impeller speed increased to provide continuous movement of the powder bed (i.e. 250RPM). The formulation was cooled and then sieved using a 710micron sieve to remove any large agglomerates, once distribution of the melt binder was complete.

Dissolution profiles were not obtained for examples 3 and 4.

Example 5

The following materials were employed in this example.

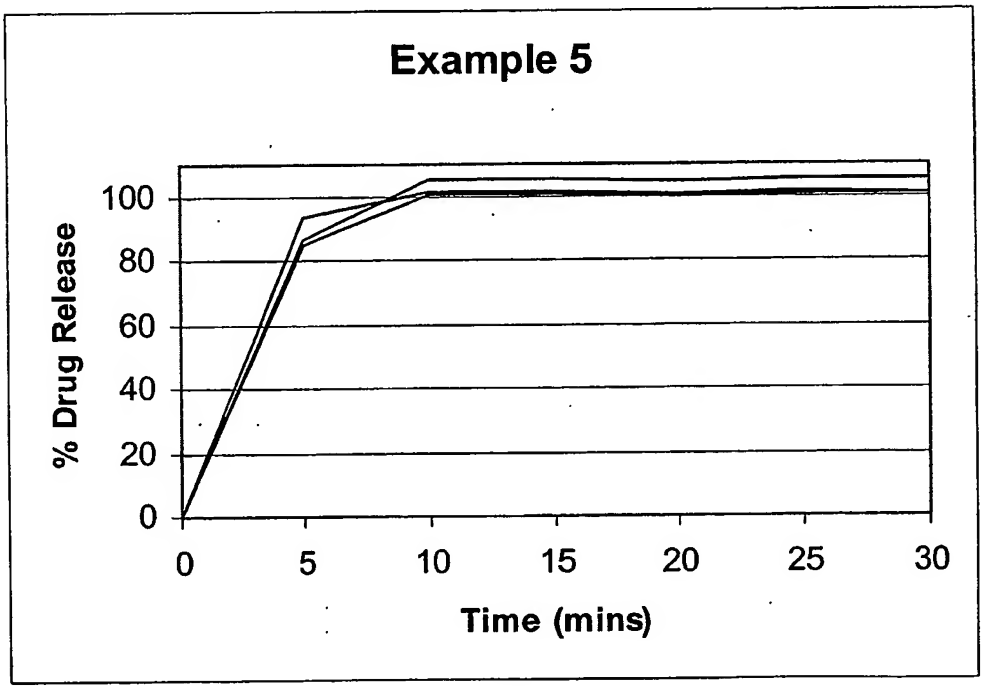
Material	% Composition
Paracetamol	82
Erythritol	5
Xylitol	10
Maltodextrin M100	2
Aspartame	0.5
Acesulphame K	0.5

Method

Granular acetaminophen and erythritol were accurately weighed into a glass jar and blended at 42rpm for 30 minutes using an inversion low shear mixer. The blend was transferred to a jacketed vessel maintained at a temperature of 121°C. The blend was mixed at an impeller speed sufficient to keep the whole powder bed moving (i.e. 222RPM) using an overhead mixer for a time sufficient to allow homogenous distribution of the molten binder in the blend. The temperature was then reduced to 95°C and the xylitol, aspartame fine, acesulphame potassium and maltodextrin added to the blend. The impeller speed was increased as required to provide continuous movement of the powder bed (i.e. 250 RPM). The formulation was cooled and then sieved using a 710micron sieve to remove any large agglomerates, once distribution of the melt binder was complete.

Results

Example 5 exhibited improved tastemasking over example 2, with improved masking of the slight aftertaste which was evident in example 3 and minimal evidence of the aftertaste which was evident in example 4. The browning of the formulation which was observed in example 3 was not evident in this formulation due to the incorporation of maltodextrin in the second stage of melt coating. The dissolution of the paracetamol from the formulation was measured using the same test as that employed in Example 1, and the results are set out below.



The drug release profiles of the formulation of Example 5 versus that of the unformulated raw drug, i.e., granular acetaminophen, are shown in Figure 1. The particle size distributions of the formulation of Example 5 ("Special Granulate APAP") versus that of the unformulated raw drug ("Paracetamol Special Granular") are shown in Figure 2.

Example 6

Example 6 describes the use of materials capable of liberating carbon dioxide in aqueous conditions to facilitate tastemasking. The following materials were employed in this example.

Material	% Composition
Paracetamol	77
Xylitol	20
Sodium Glycine Carbonate	1.2
Citric Acid Monohydrate	0.8
Acesulphame K	0.5
Aspartame	0.5

Method

Granular paracetamol, aspartame fine, sodium glycine carbonate, citric acid monohydrate, acesulphame potassium and 10% xylitol were accurately weighed into a glass jar and blended at 42rpm for 30 minutes using an inversion low shear mixer. The blend was transferred to a jacketed vessel maintained at a temperature of 95°C. The blend was mixed at an impellar speed sufficient to keep the whole powder bed moving (i.e. 222RPM) using an overhead mixer for a time sufficient to allow homogenous distribution of the molten binder in the blend. The remaining melt binder was added to the blend and the impellar speed increased to provide continuous movement of the powder bed (i.e. 250RPM). The formulation was cooled and then sieved using a 710micron sieve to remove any large agglomerates, once distribution of the melt binder was complete.

Results

The formulation exhibited acceptable tastemasking. However, the addition of Maltodextrin M100, as shown in example 7, improved its mouthfeel.

Example 7

The following materials were employed in this example.

Material	% Composition
Paracetamol	77
Xylitol	18
Maltodextrin M100	2.0
Sodium Glycine Carbonate	1.2
Citric Acid Monohydrate	0.8
Acesulphame K	0.5
Aspartame	0.5

Method

Granular paracetamol, aspartame fine, sodium glycine carbonate, citric acid monohydrate, maltodextrin M100, acesulphame potassium and 9% xylitol were accurately weighed into a glass jar and blended at 42rpm for 30 minutes using an inversion low shear mixer. The blend was transferred to a jacketed vessel maintained at a temperature of 95°C. The blend was mixed at an impeller speed sufficient to keep the whole powder bed moving (i.e. 222RPM) using an overhead mixer for a time sufficient to allow homogenous distribution of the molten binder in the blend. The remaining melt binder was added to the blend and the impeller speed increased to provide continuous movement of the powder bed (i.e.250RPM). The formulation was cooled and then sieved using a 710micron sieve to remove any large agglomerates, once distribution of the melt binder was complete.

Results

The addition of Maltodextrin M100 was shown to improve mouthfeel.

Example 8

Example 8 illustrates the use of polyethylene glycols (PEGs) as the water soluble melt binder.

The following materials were employed in this example.

Material	% Composition
Paracetamol	80
Erythritol	5
PEG6000 Powder	10
Maltodextrin M100	2.0
Sodium Glycine Carbonate	1.2
Citric Acid Monohydrate	0.8
Acesulphame K	0.5
Aspartame	0.5

Method

Granular paracetamol, erythritol, sodium glycine carbonate and citric acid monohydrate and 5% PEG6000 were accurately weighed into a glass jar and blended at 42rpm for 30 minutes using an inversion low shear mixer. The blend was transferred to a jacketed vessel maintained at a temperature of 70°C. The blend was mixed at an impeller speed sufficient to keep the whole powder bed moving (i.e. 222RPM) using an overhead mixer for a time sufficient to allow homogenous distribution of the molten binder in the blend. The remaining melt binder was added to the blend, along with the maltodextrin M100, aspartame and acesulphame potassium, and the impeller speed increased to provide continuous movement of the powder bed (i.e. 250RPM). The formulation was cooled and then sieved using a 710micron sieve to remove any large agglomerates, once distribution of the melt binder was complete.

Results

The resulting formulation exhibited reasonable tastemasking and a slight aftertaste, but with excellent mouthfeel and rapid dispersibility.

Example 9

An additional approach to drug tastemasking is described where the citric acid monohydrate content is increased to locally modify the pH within the oral cavity and therefore limit drug dissolution.

The following materials were employed in this example.

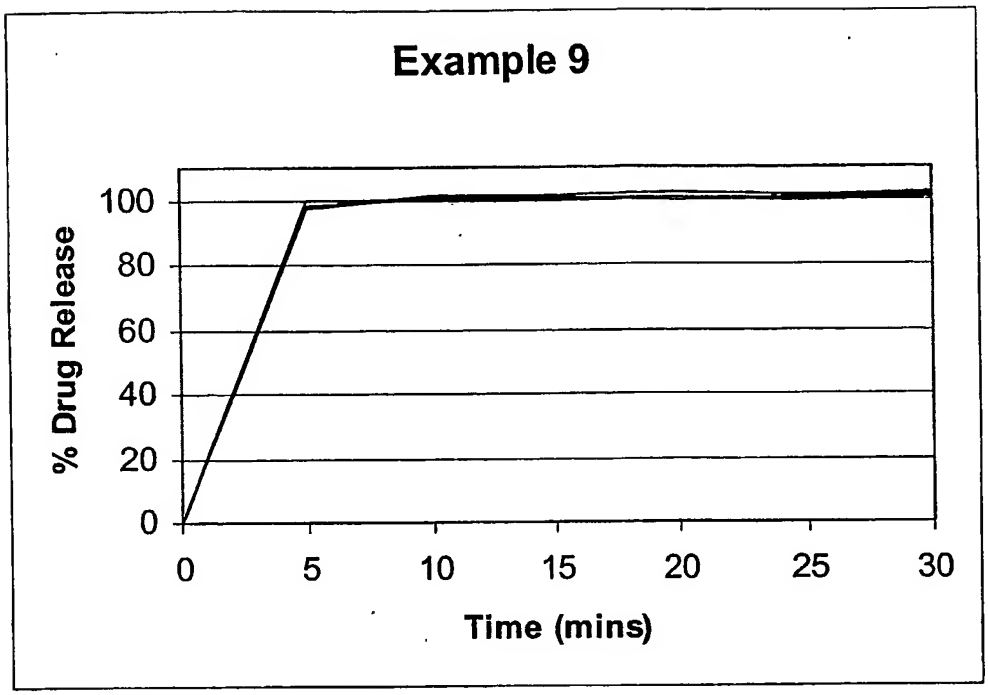
Material	% Composition
Paracetamol	77.2
Erythritol	10.0
PEG6000 Powder	7.0
Sodium starch Glycolate	2.0
Sodium Glycine Carbonate	1.2
Citric Acid Monohydrate	1.5
Acesulphame K	0.5
Aspartame	0.5
Powdered Lemon Flavour	0.1

Method

Using a Diosna P1-6 mixer-granulator equipped with a 1 litre jacketed bowl was heated at 55°C for 10 minutes before the addition of the granular acetaminophen, erythritol, sodium starch glycolate, sodium glycine carbonate, citric acid monohydrate, aspartame fine, acesulphame potassium and powdered lemon flavour. This material was blended for a further 10 minutes prior to the addition of the PEG6000. An impeller speed of 50RPM and a chopper speed of 50RPM were selected to distribute the binder through the material. Mixing was continued at the elevated temperature for approximately 5 minutes before the bowl was cooled to 25°C for 10 minutes.

Results

The resulting formulation exhibited pleasant taste, good mouthfeel and a slight bitter aftertaste; which is attributed to the presence of additional citric acid. The dissolution of the paracetamol from the formulation was measured using the same test as that employed in Example 1, and the results are set out below.



Example 10

Sumatriptan 50mg (Final Formulation Mass 75.7mg)

A granulation of Sumatriptan was prepared containing 4%w/w PVP K-30 (aqueous) in a MP Micro fluid bed dryer. The drug and binder were granulated by the addition of water, using the down-spray method. The granulated material was dried, cooled and then screened through a 250μm sieve and airjet sieved to remove particles below 100μm. The resulting granules were then spray coated with an aqueous dispersion of Eudragit RD-100 plasticised with Triacetin. The quantity of coating was sufficient to achieve the required degree of tastemasking of the active (approximately 15% weight gain). The granules were then dried and cooled for hot melt coating with xylitol. The tastemasked Sumatriptan granules were loaded into a 1 litre-jacketed bowl for a modified Diosna P1-6 mixer-granulator (preheated at 95°C for 10 minutes) with 1% Aspartame (or 0.5% Aspartame and 0.5% Acesulfame potassium) and 10% xylitol. An impeller speed of 50RPM and a chopper speed of 50RPM were selected to distribute the binder (xylitol) through the material. Mixing

was continued at the elevated temperature for approximately 5 minutes before addition of a further 10% xylitol to the system. After another 5 minutes mixing, the bowl was cooled to 25°C over 10 minutes. Once cooled the formulation was tested. It was found that improved tastemasking and drug release could be achieved by further addition of Triacetin to the Eudragit RD100 film coat.

Example 11

Lansoprazole 15mg (Final Formulation Mass 20mg)

Using a Diosna P1-6 mixer-granulator, a melt-granulation of 75% Lansoprazole, 20% PEG 6000 and 5% Aspartame was prepared using a one litre jacketed mixing bowl heated to a temperature sufficient to melt the PEG 6000 binder (i.e. 70°C). The Lansoprazole and Aspartame were equilibrated in the bowl for 10 minutes at an impeller speed of 300RPM and a chopper speed of 150RPM, after this time the PEG6000 was added and massing continued for another 3 minutes. The material was then emptied from the bowl, cooled on a metal tray at room temperature and then stored in sealed bags. It was found that incorporation of 5% of a low-viscosity Sodium Starch Glycolate into the granules improved the mouthfeel of this formulation without altering drug release or the degree of tastemasking.

Example 12

Ranitidine 150mg (Final Formulation Mass 200mg)

Using a Diosna P1-6 mixer-granulator, a melt-granulation of 75% Ranitidine, 20% PEG 6000 and 5% Aspartame was prepared using a one litre jacketed mixing bowl heated to a temperature sufficient to melt the PEG 6000 binder (i.e. 70°C). The Ranitidine and Aspartame were equilibrated in the bowl for 10 minutes at an impeller speed of 300RPM and a chopper speed of 150RPM, after this time the PEG6000 was added and massing continued for another 3 minutes. The material was then emptied from the bowl, cooled on a metal tray at room temperature and then stored in sealed bags. It was found that incorporation of molar equivalents of citric acid monohydrate and sodium bicarbonate into the melt granulation improved the degree of tastemasking and aided the dispersion of the granules.

Example 13

Domperidone 10mg (Final Formulation Mass 100mg)

A 5%w/w aqueous dispersion of maltodextrin containing 5%w/w domperidone was prepared and spray-coated onto microcrystalline cellulose spheres sufficient to achieve a 33% coating wt. gain using and MP-Micro Fluid Bed Dryer. The coated spheres were then dried and cooled for hot melt coating with xylitol. Using a modified Diosna P1-6 mixer-granulator the domperidone-loaded microcrystalline cellulose spheres were blended with 10% wt. gain of xylitol using a one litre jacketed mixing bowl heated to 95°C. An impeller speed of 50RPM and a chopper speed of 50RPM were selected to distribute the binder through the material. Mixing was continued at the elevated temperature for approximately 5 minutes before addition of a further 10% xylitol to the system. After another 5 minutes mixing, the bowl was cooled to 25°C over 10 minutes. Once cooled, the formulation was tested. It was found that the incorporation of 0.25 – 0.5% of hydroxypropylmethylcellulose to the xylitol improved the stability of the formulation.

Example 14

Paracetamol (Acetaminophen) 500mg (Final Formulation Mass 745mg)

Step 1: Spray coating with Surelease

Granular paracetamol was tastemasked by spray-coating with an aqueous dispersion of ethylcellulose in an MP-Micro Fluid Bed Dryer. Approximately a 15% wt. gain was required, depending on the degree of tastemasking. Once the desired weight of ethylcellulose had been added to the granules, the material was dried, cooled and then screened through a 250µm sieve and airjet sieved to remove particles below 100µm. Using a modified Diosna P1-6 mixer-granulator, the tastemasked paracetamol granules were then blended with 1% Aspartame and 10% xylitol in a one litre jacketed mixing bowl heated to 95°C for 10 minutes. An impeller speed of 50RPM and a chopper speed of 50RPM were selected to distribute the binder through the material. Mixing was continued at the elevated temperature for approximately 5 minutes before addition of a further 10% xylitol to the system. After another 5 minutes mixing the bowl was cooled to 25°C over 10 minutes. Once cooled the formulation was tested. It was found that improved tastemasking and

drug release could be achieved by further addition of glycerol to the ethylcellulose film coat.

Example 15

Loperamide 2mg (Final Formulation Mass 50mg)

A granulation of equal quantities of aspartame and Acesulphame K was prepared using 4%w/w PVP K-30 (aqueous) in a MP Micro fluid bed dryer. The drug and binder were granulated by the addition of water, using the down-spray method. The granulated material was dried, cooled and then screened through a 250μm sieve and airjet sieved to remove particles below 100μm. The granules were dried and cooled for hot melt coating with xylitol. Using a modified Diosna P1-6 mixer-granulator the aspartame/acesulphame K granules were blended with 4% Loperamide and 10% wt. gain of xylitol using a one litre jacketed mixing bowl heated to 95°C. An impeller speed of 50RPM and a chopper speed of 50RPM were selected to distribute the binder through the material. Mixing was continued at the elevated temperature for approximately 5 minutes before addition of a further 10% xylitol to the system. After another 5 minutes mixing the bowl was cooled to 25°C over 10 minutes. Once cooled the formulation was tested. It was found that the incorporation of 0.25 – 0.5% of hydroxypropylmethylcellulose to the xylitol improved the stability of the formulation.

Example 17

Co-Beneldopa 12.5mg/50mg (Final Formulation Mass 164.8mg)

A granulation of 19.2% Benserazide Hydrochloride and 76.8% Levodopa was prepared using 4%w/w PVP K-30 (aqueous) in a MP Micro fluid bed dryer. The drug and binder were granulated by the addition of water, using the down-spray method. The granulated material was dried, cooled and then screened through a 250μm sieve and airjet sieved to remove particles below 100μm. The granules were dried and cooled for hot melt coating with Xylitol. Using a modified Diosna P1-6 mixer-granulator the Co-Beneldopa granulation was blended with 10% xylitol in a one litre jacketed mixing bowl heated to 95°C for 10 minutes. An impeller speed of 50RPM and a chopper speed of 50RPM were selected to distribute the binder through the material. Mixing was continued at the elevated temperature for

approximately 5 minutes before addition of a further 10% xylitol to the system. After another 5 minutes mixing the bowl was cooled to 25°C over 10 minutes. Once cooled the formulation was tested. It was found that by adding a 5% wt. gain of glyceryl palmitostearate and 1% wt. gain of aspartame, the degree of tastemasking was improved without adversely impeding drug release.

Example 18

Enteric coated Aspirin formulation

Method

Granular Aspirin, having a particle size suitable for spray coating (i.e., between 100 and 500μm) was coated in an MP-Micro fluid bed dryer, using the down-spray coating module. An aqueous dispersion of 15%w/w Opadry® was prepared, which was sprayed onto the granular aspirin at a product temperature of between 40 and 45°C to a weight gain of 10%. The coated material was dried before a 15% weight gain of an aqueous dispersion of 15%w/w Acryl-eze was added to the granules, at a product temperature of 25 – 35°C. The material was dried and cooled before being placed in a one litre jacketed bowl for the Diosna P1-6 mixer granulator. A blend of 60% enteric coated aspirin, 20% Mannitol, 10% Xyltiol 7% Peg 6000, 0.5% Aspartame, 0.5% Acesulfame Potassium and 2% Maltodextrin was equilibrated at 70°C whilst mixing at an impellar speed of 50RPM and a chopper speed of 50RPM. Mixing was continued at the elevated temperature for approximately 5 minutes before the bowl was cooled to 25°C for 10 minutes.

Results

The formulation met USP requirements for acid phase drug release, i.e., less than or equal to 10% dissolved in 2 hours in 0.1M HCl and greater than 80% released in 90 minutes in pH 6.8 phosphate buffer.

Example 19

Controlled Release Chlorpheniramine Maleate Drug-loaded Spheres

Step 1: Drug Loading

Chlorpheniramine maleate was dissolved in an aqueous dispersion of 10% Opadry®. A 15% weight gain of Opadry® was applied to 60-40mesh non-pariel sugar spheres,

in order to obtain an active drug content of approximately 8%w/w. The dispersion was applied to the sugar spheres at a product temperature of between 40 and 45°C in an MP-Micro fluid bed dryer, using the down-spray coating module.

Step 2: Sustained release coating

An additional 5% coat of 10% Opadry® aqueous dispersion was added to the drug loaded spheres before the application of an aqueous dispersion of 15%w/w Surelease was applied. A weight gain of between 15 and 30% was applied to produce a formulation with the required release profile.

Step 3: Melt Granulation

The dried, 65% drug-loaded spheres were blended in a one litre jacketed bowl for the Diosna P1-6 mixer granulator with 15% Mannitol, 10% Erythritol, 7% Peg 6000, 0.5% Aspartame, 0.5% Acesulfame Potassium and 2% Maltodextrin and equilibrated at 70°C whilst mixing at an impellar speed of 50RPM and a chopper speed of 50RPM. Mixing was continued at the elevated temperature for approximately 5 minutes before the bowl was cooled to 25°C for 10 minutes.

Results

Time (Hours)	% Drug Release
2	20 – 30
4	35 - 45
6	45 – 55
12	60 - 70

Example 20

Immediate release Chlorpheniramine Maleate

A granulation of 8% Chlorpheniramine Maleate, 4%w/w PVP K-30 and 88% Xylitol was prepared in an MP Micro fluid bed dryer. The materials were granulated by the addition of water, using the down-spray method. The granulated material was dried, cooled and then screened through a 250μm sieve and airjet sieved to remove particles below 100μm. A blend containing 50% Chlorpheniramine Granules, 25%

Granular Mannitol, 10% Erythritol, 0.5% Aspartame, 0.5% Acesulfame Potassium, 1.2% Citric Acid Monohydrate, 0.8% Sodium Glycine Carbonate and 2% Maltodextrin was equilibrated at 70°C in a one litre jacketed bowl for a Diosna P1-6 mixer-granulator for 10 minutes at an impellar speed of 50RPM and a chopper speed of 50RPM prior to the addition of 10% PEG6000. Mixing was continued at the elevated temperature for approximately 5 minutes before the bowl was cooled to 25°C for 10 minutes.

Example 21

Chronotherapeutic Chlorpheniramine Maleate Blend

Method

A blend of 16.7g of immediate-release chlorpheniramine maleate granules (Example 20) was blended with 83.3g controlled-release chlorpheniramine maleate drug-loaded spheres (Example 19) at 42rpm for 30 minutes using an inversion low shear mixer.

Results (Formulation mass 600mg: active 24mg)

Time (Hours)	Mean Drug Release (mg) n=6
0.5	4.2
4	9.6
6	12.1
12	15.6

Claims

1. A drug formulation for gastrointestinal deposition, said formulation comprising a free flowing plurality of particles comprising an active agent and a water-soluble excipient, wherein the particles have a mean diameter of greater than about 10 μm to about 1 mm, and the formulation is capable of dissolving or dispersing in a patient's mouth within 1 minute after administration without the co-administration of a fluid.

2. A drug formulation for gastrointestinal deposition, said formulation comprising a free flowing plurality of particles and including an active agent and a water-soluble excipient, wherein the particles have a mean diameter of greater than about 10 μm to about 1 mm, and the excipient has a negative heat of solution.

3. A drug formulation as claimed in claim 2, wherein said particles each include both active agent and water-soluble excipient.

4. A drug formulation as claimed in claim 3, wherein the particles comprise a core and a coating that includes a quantity of the excipient.

5. A drug formulation as claimed in any of the proceeding claims, wherein the particles are formed by melt-coating core particles with a coating material that includes a quantity of the excipient, at a temperature below the melting point or decomposition temperature of the active agent.

6. A drug formulation as claimed in claim 4 or 5, wherein a quantity of the active agent is included in the core or core particles.

7. A drug formulation as claimed in claim 6, wherein the coating or coating material is substantially free of active agent.

8. A drug formulation as claimed in claim 4, 5 or 6, wherein a quantity of the active agent is included in the coating or coating material.

9. A drug formulation as claimed in claim 8, wherein the core or core particles are substantially free of active agent.

10. A drug formulation as claimed in any of claims 4-9, wherein the coating or coating material further comprises a water soluble or hydrophilic binder.

11. A drug formulation as claimed in claim 10, wherein the binder melts or softens sufficiently to melt-coat the core particles at a temperature below the melting point or decomposition temperature of the active agent.

12. A drug formulation as claimed in any of claims 1-11, wherein the excipient melts or softens sufficiently to melt-coat the core particles at a temperature below the melting point or decomposition temperature of the active agent.

13. A drug formulation as claimed in claim 11, wherein the binder melts or softens sufficiently to melt-coat the core particles at a temperature below the melting point or decomposition temperature of the excipient.

14. A drug formulation as claimed in any of claims 4-13, wherein the coating or coating material substantially completely covers the surface of the core or core particles.

15. A drug formulation as claimed in any of the preceding claims, wherein the core or core particles include a quantity of the water-soluble excipient and/or an additional, optionally, water soluble excipient.

16. A drug formulation as claimed in claim 15, wherein, the core or each core particle comprises a granulation of said an additional excipient and active agent, or a particle of additional excipient coated with active agent.

17. A drug formulation as claimed in any of the preceding claims, formed by a process in which the active agent is not raised to or above its melting point, or a temperature at which a significant proportion thereof is caused to decompose.

18. A drug formulation as claimed in any of the preceding claims, wherein the melting point of the water-soluble excipient is equal to or below 150, 120 or 110°C.

19. A drug formulation as claimed in claim 18, wherein the melting point of the water-soluble excipient is at least 40 or 50°C.

20. A drug formulation as claimed in any of the preceding claims, wherein the melting point of the binder is equal to or below 150, 120 or 110°C.

21. A drug formulation as claimed in claim 20, wherein the melting point of the binder is at least 40 or 50°C.

22. A drug formulation as claimed in any of the preceding claims, wherein the melting point of the excipient exceeds that of the binder.

23. A drug formulation as claimed in any of the preceding claims, wherein the water-soluble excipient has a heat of solution equal to or below –7KCal/Kg.

24. A drug formulation as claimed in claim 23, wherein the heat of solution of the water-soluble excipient is equal to or below –10, -15, -20, -25, or -30KCal/Kg.

25. A drug formulation as claimed in any of the preceding claims, wherein the solubility in water of the water-soluble excipient is at least 20, 30 or 40% w/w at 25°C.

26. A drug formulation as claimed in any of the preceding claims, wherein the water-soluble excipient is a sugar, sugar alcohol, polyethylene glycol (PEG), polyethylene oxide, gelatin, partially hydrolyzed gelatin, hydrolyzed dextran, dextrin, alginate or a mixture of any of the foregoing.

27. A drug formulation as claimed in claim 26, wherein the water-soluble excipient is a sugar alcohol or combination of sugar alcohols.

28. A drug formulation as claimed in claim 27, wherein the sugar alcohol or sugar alcohols is or are sorbitol, mannitol, maltitol, reduced starch saccharide, xylitol, reduced paratinose, erythritol, or any combination thereof.

29. A drug formulation as claimed in any of the preceding claims, wherein the binder includes a polyethylene glycol (PEG) and/ or a polyethylene oxide.

30. A drug formulation as claimed in any of the preceding claims, wherein the core or core particles include an additional excipient for controlling or delaying the release of the active agent.

31. A drug formulation as claimed in claim 30, wherein the core or core particles include a layer or coating of said additional excipient encapsulating an inner core comprising the active agent.

32. A drug formulation as claimed in claim 30 or 31, wherein said additional excipient provides an enteric or sustained release coating.

33. A drug formulation as claimed in claim 32, wherein said additional excipient is selected from the group consisting of cellulose acetate phthalate, hydroxypropyl-methylcelluose phthalate, polymethacrylates, Shellac, ethylcellulose, hydroxypropyl-celluose, and hydroxypropylmethylcelluose.

34. A drug formulation as claimed in any of the preceding claims, wherein said formulation dissolves in a patient's mouth within 30 or 15 seconds after administration without the coadministration of a fluid.

35. A drug formulation as claimed in any of the preceding claims, wherein the particles comprise at least about 50%, 60%, or 75% drug.

36. A drug formulation as claimed in any of the preceding claims further comprising a salivary stimulant.

37. A drug formulation as claimed in any of the preceding claims, wherein said formulation further comprises an excipient selected from the group consisting of polyvinyl alcohol, polyvinylpyrrolidine, acacia and combinations thereof.

38. A drug formulation as claimed in any of the preceding claims further comprising a water-soluble artificial sweetener.

39. A drug formulation as claimed in claim 38, wherein said water soluble artificial sweetener is selected from the group consisting of soluble saccharin salts, such as sodium or calcium saccharin salts, cyclamate salts, acesulfam-K, the free acid form of saccharin and mixtures thereof.

40. A drug formulation as claimed in any of the preceding claims further comprising a dipeptide based sweetener.

41. A drug formulation as claimed in claim 40, wherein said dipeptide based sweetener is L-aspartyl L-phenylalanine methyl ester.

42. A drug formulation as claimed in claim 36, wherein said salivary stimulant is selected from the group consisting of citric acid, tartaric acid, malic acid, fumaric acid, adipic acid, succinic acid, acid anhydrides thereof, acid salts thereof and combinations thereof.

43. A drug formulation as claimed in claim 36, wherein said salivary stimulant is an effervescent agent.

44. A drug formulation as claimed in claim 43, wherein said effervescent agent is the result of a reaction of a soluble acid source and an alkali metal carbonate or carbonate source.

45. A drug formulation as claimed in claim 2 or claim 3, wherein the formulation is capable of dissolving or dispersing in a patient's mouth within 1 minute after administration without the co-administration of a fluid.

46. A drug formulation as claimed in any of the preceding claims, arranged for direct un-encapsulated administration to the oral cavity.

47. A drug formulation as claimed in any of the preceding claims, wherein the particles are non-compressed.

48. A method of preparing a drug formulation as claimed in any of the preceding claims, comprising forming the particles by melt-coating core particles with a coating material that includes a quantity of the water-soluble excipient and, optionally, a quantity of the binder, at a temperature below the melting point or decomposition temperature of the active agent.

49. Use of a drug formulation as claimed in any of claims 1-47, or a drug formulation prepared by a method as claimed in claim 48, for the preparation of a medicament for treating a human or animal patient, wherein the formulation is administered directly and in an un-encapsulated form to the patient's oral cavity.

50. A method of treating a human or animal patient, wherein a formulation as claimed in any of claims 1-47, or a drug formulation prepared by a method as claimed in claim 48, is administered in a un-encapsulated form directly into the patient's oral cavity.

51. A drug delivery system comprising a dosing device comprising a housing and an actuator, said device containing at least one unit dose of a drug formulation as claimed in any one of claims 1-47, or a drug formulation prepared by a method as claimed in claim 48, said device upon actuation delivering a unit dose of said drug formulation such that an effective dose of said drug cannot be delivered into the lower lung of a human patient.

52. The drug delivery system of claim 51 wherein said at least one unit dose is contained in a reservoir.

53. The drug delivery system of claim 51 further comprising a metering component to meter a unit dose from said reservoir upon actuation of said system.

54. The drug delivery system of claim 51 comprising multiple unit doses, wherein said unit doses are individually metered prior to said actuation.

55. The drug delivery system of claim 51 further comprising sachets, each sachet containing said individually metered unit dose.

56. The drug delivery system of claim 55 wherein said sachets are aligned linearly in the form of a strip.

57. The drug delivery system of claim 56 wherein said strip is in the form of a roll.

58. The drug delivery system of claim 57 further comprising blisters on a substrate base, each blister containing said individually metered unit dose, said blisters covered by a seal.

59. The system of claim 58 wherein said blisters are aligned linearly in the form of a strip.

60. The system of claim 59 wherein said strip is in the form of a roll.

61. A method of treating a patient with an active agent for gastrointestinal deposition comprising administering a formulation comprising a non-compressed free flowing plurality of particles comprising an active agent and a water-soluble excipient, said particles having a mean diameter of greater than 10 μm to about 1 mm, and said formulation dissolving in a patient's mouth within 1 minute after administration without the co-administration of a fluid.

62. A method of treating a patient with an active agent for gastrointestinal deposition comprising formulating a drug formulation comprising a non-compressed free flowing plurality of particles comprising an active agent and a water-soluble excipient, said particles having a mean diameter of greater than 10 μm to about 1 mm, and said formulation dissolving in a patient's mouth within 1 minute after administration without the co-administration of a fluid, containing said drug formulation in a drug delivery, said device upon actuation delivering a unit dose of said drug formulation such that an effective dose of said drug cannot be delivered into the lower lung of a human patient; and administering a unit dose of said particles to the oral cavity.

63. A method of preparing a drug delivery system for gastrointestinal deposition of an active agent comprising formulating a drug formulation comprising a non-compressed free flowing plurality of particles comprising an active agent and a water-soluble excipient, said particles having a mean diameter of greater than 10 μm to about 1 mm, and said formulation dissolving in a patient's mouth within 1 minute after administration without the coadministration of a fluid, containing said drug formulation in a drug delivery, said device upon actuation delivering a unit dose of said drug formulation such that an effective dose of said drug cannot be delivered into the lower lung of a human patient.

64. The system or method of claims 51-63 wherein said active agent is an antibiotic.

65. The system or method of claim 64 wherein said antibiotic is a macrolide antibiotic.

66. The system or method of claim 65 wherein said macrolide antibiotic is selected from the group consisting of erythromycin, dirithromycin, josamycin, midecamycin, kitasamycin, tylosin, roxithromycin, rokitamycin, oleandomycin, miocamycin, flurithromycin, rosaramicin, azithromycin, clarithromycin, and pharmaceutically acceptable salts thereof.

67. The system or method of claim 65 wherein said macrolide antibiotic is selected from the group consisting of erythromycin, clarithromycin, and pharmaceutically acceptable salts thereof

68. A method of treating a patient with a macrolide antibiotic for gastrointestinal deposition comprising administering a drug formulation for gastrointestinal deposition comprising a non-compressed free flowing plurality of particles comprising a macrolide antibiotic and a water-soluble excipient, said particles having a mean diameter of greater than 10 μm to about 1 mm, said formulation dissolving in a patient's mouth within 1 minute after administration without the coadministration of a fluid.

69. The method of claim 68 wherein said formulation dissolves in a patient's mouth within 30, or 15 seconds after administration without the coadministration of a fluid.

70. The method of claim 68 wherein said particles comprise at least about 50%, 60% or 75% drug.

71. A macrolide antibiotic formulation for gastrointestinal deposition comprising a non-compressed free flowing plurality of particles comprising a macrolide antibiotic and a water-soluble excipient, said particles having a mean diameter of greater than 10 μm to about 1 mm, said formulation dissolving in a patient's mouth within 1 minute after administration without the coadministration of a fluid.

72. A formulation for gastrointestinal deposition comprising a non-compressed free flowing plurality of particles comprising an active agent and a water-soluble excipient, said particles having a mean diameter of greater than 10 μm to about 1 mm, said formulation dissolving in a patient's mouth within 1 minute after administration without the co-administration of a fluid, said particles comprising less than 5% hydrophobic material.

73. The formulation of claim 72 wherein said particles are prepared by a process comprising melt granulating said water soluble excipient and the active agent to form a homogenous mixture.

74. The formulation of claim 72 wherein said particles are prepared by a process comprising melt coating said water soluble excipient onto said active agent.

75. The formulation of claims 73 and 74 which are prepared without the use of an aqueous fluid.

76. A drug formulation as claimed in any of claims 1-48, wherein the water-soluble excipient is xylitol

77. A drug formulation as claimed in any of claims 1-48, wherein the active agent is paracetamol.

78. A drug formulation as claimed in any one of claims 1-48, being adapted to provide both immediate release and controlled release of the active agent.

79. A drug formulation as claimed in claim 78, comprising a free flowing plurality of particles comprising an active agent and a water-soluble excipient, wherein at least a portion of the particles comprise active agent and at least one delayed release excipient.

80. A drug formulation as claimed in claims 78 and 79, wherein a first portion of the particles comprises at least one delayed release excipient, to provide controlled release of active agent, and a second portion of the particles does not include any delayed release excipients, to provide immediate release of active agent.

Fig. 1

Drug release profile of Example 5 Vs Unformulated Drug

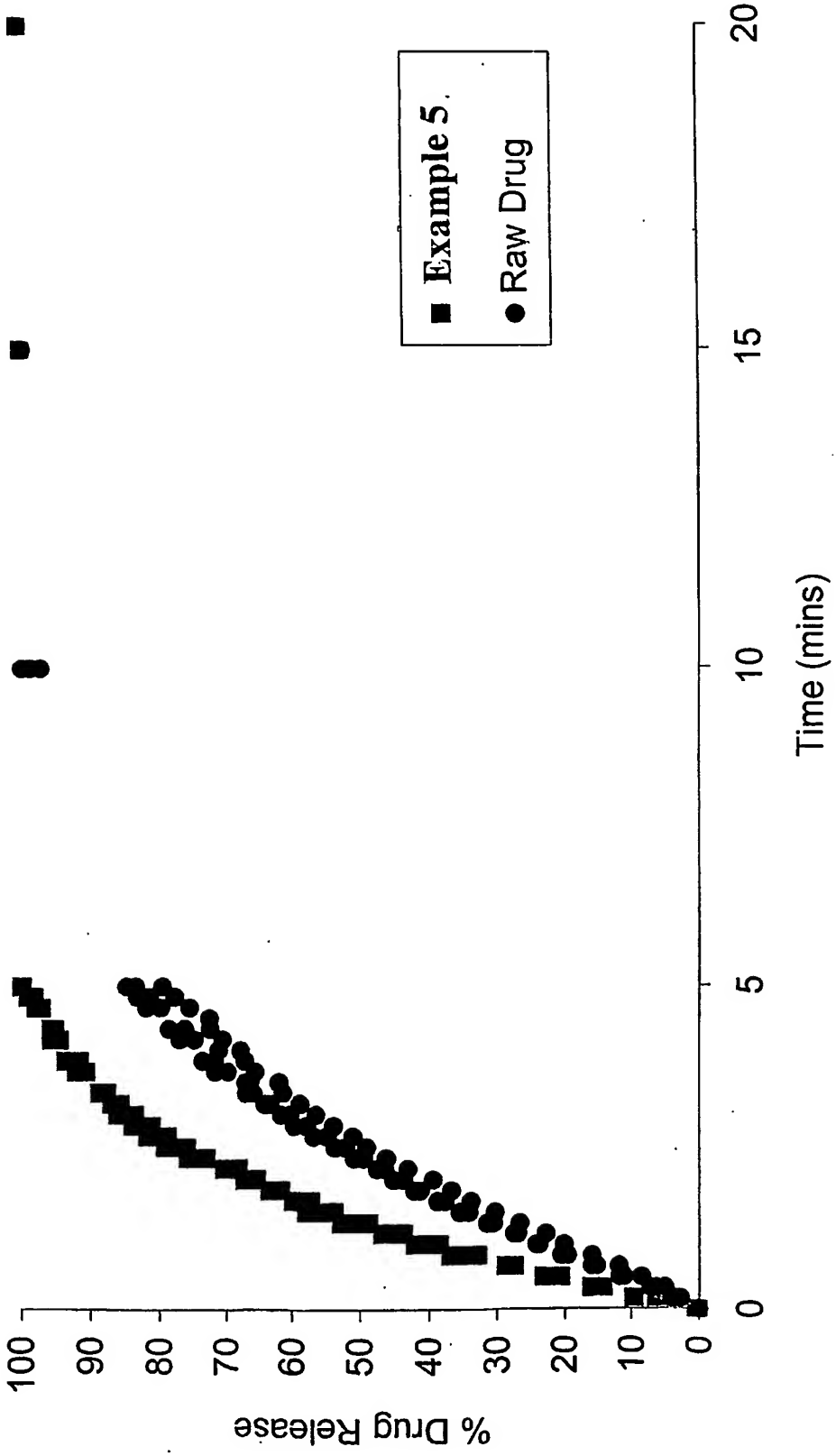
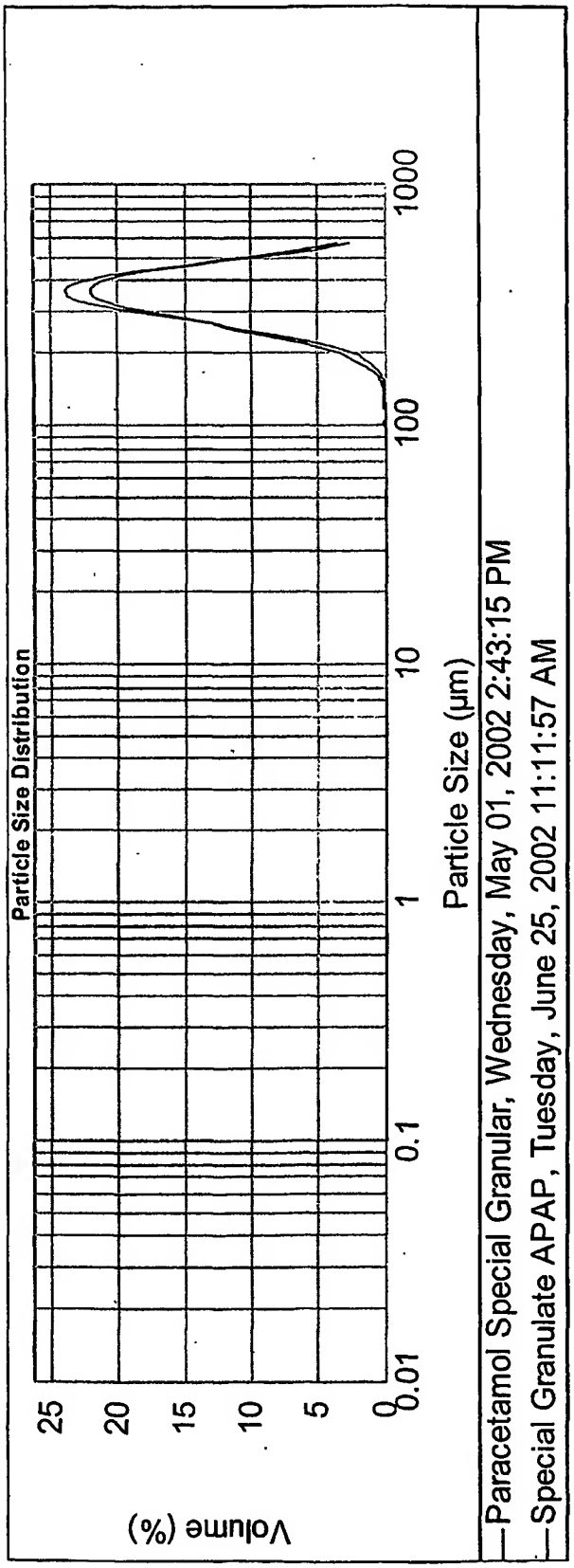


Fig. 2


Particle Size Distribution
Volume (%)
25
20
15
10
5
0
0.01
0.1
1
10
100
1000
Particle Size (µm)
Paracetamol Special Granular, Wednesday, May 01, 2002 2:43:15 PM
Special Granulate APAP, Tuesday, June 25, 2002 11:11:57 AM

INTERNATIONAL SEARCH REPORT

Internat Application No
PCT/GB 03/00969

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K9/14 A61K9/16 A61K9/46 A61J1/03 A61J7/00
A61K31/7048 A61K31/167

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, EMBASE, BIOSIS, FSTA

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2001/020147 A1 (TOBYN MICHAEL ET AL) 6 September 2001 (2001-09-06) cited in the application page 2, paragraphs 15-28 page 3, paragraphs 35-40 page 4, paragraphs 43-48,53-55 page 6-9; claims 1-91 ---	1-80
X	US 5 607 697 A (SANFTLEBEN RONALD A ET AL) 4 March 1997 (1997-03-04) column 1, line 49 -column 2, line 12 column 2, line 51 -column 4, line 67 column 6, line 12 -column 10, line 13 claims 1-11; examples 1,2,6 --- -/--	1-80

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
17 June 2003	25/06/2003

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Houyvet, C

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Internat Application No
PCT/GB 03/00969

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	US 3 887 700 A (BONCEY GRAHAM ARTHUR ET AL) 3 June 1975 (1975-06-03) column 1, line 64 -column 2, line 54 column 3, line 31-36 column 4, line 3-15,26-31,53-66; examples 1-4	1-80
Y	EP 0 966 952 A (CERESTAR HOLDING BV) 29 December 1999 (1999-12-29) page 2, paragraphs 1-6,11	1-80
Y	EP 0 727 146 B (CERESTAR HOLDING BV) 21 August 1996 (1996-08-21) page 2, paragraphs 1,2,5,6 page 3, paragraph 18	1-80
P,X	EP 1 219 291 A (MCNEIL PPC INC) 3 July 2002 (2002-07-03) page 2, paragraphs 1,5,6 page 3, paragraphs 12-15 page 5, paragraphs 34,35 page 6, paragraphs 40,41 claims 1-11; example 2	1-80
E	WO 03 020241 A (SIMPSON DAVID BRADLEY BROOK ;TOBYN MICHAEL (GB); VECTURA LTD (GB);) 13 March 2003 (2003-03-13) page 1, paragraph 1 page 3, paragraph 11 page 4, paragraph 12 -page 12, paragraph 62 page 14, paragraph 76 -page 15, paragraph 79 page 19, paragraph 91 page 20, paragraph 96 -page 24, paragraph 113 page 27, paragraphs 122-124 page 29, paragraph 13131 -page 30, paragraph 136 page 31, paragraph 140 -page 38, paragraph 156 example 5	1-80

INTERNATIONAL SEARCH REPORT

Int onal application No.
rCT/GB 03/00969

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 49-50, 61-70
because they relate to subject matter not required to be searched by this Authority, namely:

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy : present claims 49-50, 61-70 are method of treatment where no disease is defined.

2. [X] Claims Nos.: 1-25, 30-32, 34, 45, 51, 71-72, 79-80 (all in part)
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-25, 30-32, 34, 45, 51, 71-72, 79-80 (all in part)

Present claims 1-80 relate to an extremely large number of possible formulations and drug delivery devices. In fact, the claims contain so many options, variables and possible permutations that a lack of clarity and/or conciseness within the meaning of Article 6 PCT arises to such an extent as to render a meaningful search of the claims impossible.

Further, present claims 1-2, 11-13, 17, 34, 45, 51 and 71-72 relate to drug formulations or drug delivery devices defined by reference to a desirable characteristic or property and/or result to be achieved (namely : "... capable of dissolving or dispersing in a patient's mouth within 30 or 15 seconds or 1 minute after administration..."; "...the excipient has a negative heat of solution"; "...binder/excipient melts or softens sufficiently to melt-coat ... at a temperature below the melting-point or decomposition temperature ..."; "...drug can not be delivered into the lower lung of a human patient" and "for gastrointestinal deposition"). These claims are therefore unclear (Article 6 PCT). Moreover, they cover all drug formulations and drug delivery devices having these characteristics or properties, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such formulations and devices.

Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to claims 26-29, 33, 35-44, 46-48, 52-60 and 73-78 and the examples.

Finally, in view of the large number and also the wording of the claims presently on file, it renders difficult, if not impossible, to determine the matter for which protection is sought (see also Rule 6.1(a) PCT).

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Interna Application No
PCT/GB 03/00969

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2001020147 A1	06-09-2001	AU 3400501 A	12-09-2001
		BR 0108730 A	05-11-2002
		CA 2401288 A1	07-09-2001
		EP 1261316 A2	04-12-2002
		WO 0164182 A2	07-09-2001
		NO 20024072 A	25-10-2002
US 5607697 A	04-03-1997	NONE	
US 3887700 A	03-06-1975	AT 302533 B	25-10-1972
		BE 759520 A1	30-04-1971
		CA 948108 A1	28-05-1974
		DE 2058434 A1	03-06-1971
		DK 130453 B	24-02-1975
		ES 385974 A1	01-05-1973
		FR 2073431 A5	01-10-1971
		GB 1287475 A	31-08-1972
		IE 34756 B1	06-08-1975
		IL 35714 A	14-03-1974
		IN 129401 A1	16-08-1975
		JP 51006727 B	02-03-1976
		MX 3244 E	06-08-1980
		NL 7017417 A ,B,	02-06-1971
		OA 3600 A	30-03-1971
		SE 383099 B	01-03-1976
		US 3882228 A	06-05-1975
		ZA 7007915 A	25-08-1971
		ZM 13470 A1	22-11-1971
EP 0966952 A	29-12-1999	EP 0966952 A1	29-12-1999
		JP 2000004806 A	11-01-2000
		US 6066345 A	23-05-2000
EP 0727146 B	21-08-1996	AT 195632 T	15-09-2000
		CA 2169244 A1	15-08-1996
		DE 69609874 D1	28-09-2000
		DE 69609874 T2	28-12-2000
		DK 727146 T3	18-09-2000
		EP 0727146 A2	21-08-1996
		ES 2149424 T3	01-11-2000
		FI 960657 A	15-08-1996
		GR 3034522 T3	29-12-2000
		JP 8242769 A	24-09-1996
		NO 960570 A	15-08-1996
		PT 727146 T	29-12-2000
		US 6143345 A	07-11-2000
EP 1219291 A	03-07-2002	US 2002119196 A1	29-08-2002
		AU 9736101 A	27-06-2002
		CA 2365844 A1	21-06-2002
		CN 1366878 A	04-09-2002
		EP 1219291 A1	03-07-2002
		JP 2002272817 A	24-09-2002
WO 03020241 A	13-03-2003	WO 03020241 A2	13-03-2003